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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 725.1049

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on _____

Signature _____

Typed or printed name _____

Application Number	Filed
10/554,410	2005-11-17

First Named Inventor: Paganelli

Art Unit	Examiner
1643	Gussow, A.

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☑ attorney or agent of record.
Registration number 48,265.

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

/Silvia Salvadori/
Signature

Silvia Salvadori
Typed or printed name

646-783-6758
Telephone number

August 5, 2010
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☑ *Total of 1 forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES PATENT & TRADEMARK OFFICE

Applicant:	Paganelli et al	Confirmation No.:	4581
Art Unit:	1643		
Serial No.:	10/554,410		
Filed:	November 17, 2005		
Examiner:	Gussow, Anne		
For:	**MEDICAMENT FOR THE TWO-STEP PERIOPERATIVE THERAPY OF SOLID TUMORS**		

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

PRE-APPEAL BRIEF

Sir:

Applicants submit this Pre-Appeal Brief together with a Notice of Appeal in the above-identified patent application.

REMARKS

All of the pending claims 1, 3-7, 9, 11-14 and 18-39 are the subject of Applicants' appeal. The presently claimed invention is directed to:

> A method of treating a patient with a solid tumor, said method comprising:
> (a) administering intraoperatively via a locoregional route to said patient a first agent endowed with tumor tropism, wherein said first agent is selected from the group consisting of avidin, streptavidin, their polymeric derivatives and their derivatives with polyethylene glycol capable of concentrating locally on the tumor or in the vicinity of it and then
> (b) administering postoperatively via a systemic route a second anticancer agent with affinity for said first agent,
> whereby increased accumulation of said first agent endowed with tumor tropism reduces the amount of said second anticancer agent to be administered.

(*e.g.*, page 8, lines 12-15 and lines 17-24).

The presently claimed invention is directed to a method of treating a patient with solid tumor by first administering intraoperatively a first agent as avidin, streptavidin, etc and then administering postoperatively a second anticancer agent having affinity for the first agent. Because avidin is endowed with tumor tropism, the presently claimed invention can be successfully used on tumors which do not express antigens (*e.g.*, page 8 lines 16-18).

The Examiner has rejected the pending claims under 35 U.S.C. § 103(a) for allegedly being obvious over a combination of Rusckowski et al. (Journal of Nuclear Medicine, 1996, Vol. 37, pages 1655-1662, hereinafter "Rusckowski"), or Samuel et al. (Journal of Nuclear Medicine, 1996, Vol. 37, pages 55-61, hereinafter "Samuel") in view of Goldenberg (U.S. Patent Application Publication No. 2001/0006618, hereinafter "Goldenberg"), Cokgor et al. (Journal of Clinical Oncology, 2000, Vol. 18, pages 3862-3872, hereinafter "Cokgor") and MacPhee et al. (U.S. Patent No. 6,054,122, hereinafter "MacPhee").

As submitted in the response filed on March 2, 2010 (*e.g.*, from page 2 line 21 to page 3 line 5), Rusckowski does not belong to the field of anticancer treatment, but rather to the field of

imaging osteomyelitis. Further, Rusckowski provides for both avidin and streptavidin being administered intravenously ("i.v."), whereas unlabeled streptavidin is injected first and is allowed to accumulate nonspecifically into the bone lesions (*e.g.*, 1656, left col. lines 38-40, and page 1655, right col. lines 12-16). Additionally, it also discloses that biotin alone is sufficient for detecting the lesions (*e.g.*, page 1659, right col. first paragraph).

Samuel also does not belong to the anti-cancer treatment field and it describes a method to detect vascular graft infections by i.v. injection of streptavidin followed by labeled biotin. Samuel, as Rusckowski above, also describes that avidin does not have any specificity for the sites of inflammation (*e.g.*, page 55, left col first paragraph and right col, second full paragraph).

Goldenberg provides for a method for injecting a patient with either streptavidin- or avidin-conjugated antibodies, which specifically bind markers produced by or associated with the lesions (*e.g.*, paragraphs [0003] and [0036]).

Cokgor discloses the administration of I-131 labeled antibody administered into surgically created resection cavities because the systemic administration of radiolabelled antibodies have been shown to be ineffective in crossing the blood-brain barrier (*e.g.*, page 3862, right col. lines 11-15).

Finally MacPhee simply discloses a fibrin sealant dressing which could be supplemented with a number of drugs to prevent infections, inflammations, etc (*e.g.*, the abstract).

Accordingly, it is respectfully submitted that for the following reasons the combination of the cited references cannot render obvious the claimed subject matter. As an initial matter, Rusckowski or Samuel are completely silent with regard to tumors, and with regard to introduction during surgery of an agent endowed with tumor tropism, that is, of an agent capable of specifically concentrating on the tumor cell or in its vicinity (*e.g.*, page 4, lines 11-16 of the

March 2, 2010 response and specification, page 4, last paragraph). Goldenberg is also silent with regard to introducing the first agent during surgery and inherently admits that streptavidin and/or biotin lack tumor-specificity. Accordingly, the teachings of Goldenberg cannot be successful unless the tumors express specific antigens. Further, Goldenberg teaches to administer a first "composition" which comprises either streptavidin etc. conjugated with an antibody and a second composition comprising either avidin or biotin, or, as a possible variation, a biotinylated antibody in conjunction with a second composition comprising a biotin-conjugated fluorescent agent or a dye. Thus, unlike in the presently claimed invention, Goldenberg describes a first composition whose tumor specificity is conferred by the conjugated antibody (*e.g.*, [0036]-[0037].

Thus, Applicants assert that the Examiner' s comment on page 4, lines 11-14 after the "Response to Arguments" section in the pending Final Office Action is incorrect. Goldenberg does not teach that biotin could be administered without antibody 24 hours before the avidin compound. Rather, it teaches a 3-step biotin-avidin procedure in which a biotinylated antitumor antibody is injected parenterally followed by avidin and later by a biotin derivative labeled with the detection or therapy isotope (*e.g.*, [0062]).

Finally, it should be noted that Goldenberg is directed to detection of tumors to permit accurate resection, and/or tumor removal (*e.g.*, [0021]). On the other hand, the presently claimed invention confers the advantage to control tumor recurrences because it permits to drastically reduce the time elapsing from the removal of the primary tumor and the beginning of the subsequent adjuvant therapy (*e.g.*, page 3, line 10 and page 5 lines 1-3).

Accordingly, Applicants assert that for all of the reasons set forth above, the combination of the cited references does not teach all of the claimed limitations and a person skilled in the art

would find no motivation to modify and combine the teachings of Rusckowski or Samuel with Goldenberg, Cokgor and MacPhee to arrive at the presently claimed invention. Further, since none of the cited references, alone or in combination teaches a first agent endowed with tumor tropism administered intraoperatively, a person skilled in the art would have no reasonable expectation of success to arrive at the presently claimed invention by combining streptavidin administered i.v. for detection of osteomyelitis or vascular graft injection, with streptavidin- or biotin-conjugated with an antibody administered i.v., in view of iodine-131 labeled antitenascin monoclonal antibody injected into surgically created resection cavities, and further in view of a fibrin sealant dressing supplemented with antibodies, antimicrobial compositions, etc.

Accordingly, Rusckowski or Samuel cannot be combined with Goldenberg, Cokgor and MacPhee as proposed by the Examiner. Therefore, Applicants respectfully submit that the Examiner's rejection is untenable and should be overturned.

For the foregoing reasons, it is respectfully submitted that this application is in condition for an allowance and reconsideration and allowance are respectfully requested.

Should any extensions of time or fees be necessary in order to maintain this Application in pending condition, the Director is authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 02-2275.

Respectfully submitted,

LUCAS & MERCANTI, LLP

Dated: August 5, 2010

/Silvia Salvadori/

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